Symbolic Methods in Bifurcation Analysis

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Overview

2008–2012 Hopf Bifurcations in a Gene Regulatory Network

Real Quantifier Elimination by Virtual Substitution

2012–2016 Hopf Bifurcations with Larger Models, Including MBO and MAPK

Convex Coordinates

Subtropical Real Root Finding

2016– Parametric Saddle-node Bifurcations with Another Model of MAPK

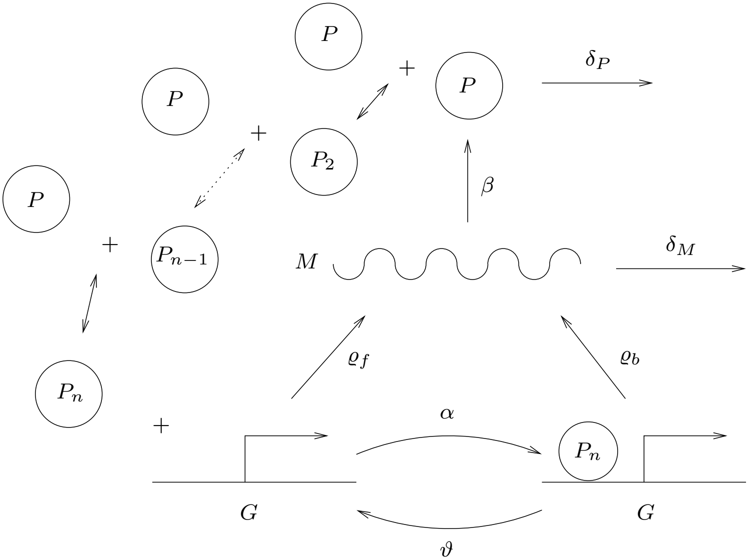
Cylindrical Algebraic Decomposition

Graph-theoretical Preprocessing

2008–2012

Hopf Bifurcations in a Gene Regulatory Network

Boulier et al., Algebraic Biology 2007



The Reaction System

$$
\begin{aligned}
G + P_n &\underset{\vartheta}{\overset{\alpha}{\rightleftarrows}} G : P_n \\
G &\xrightarrow{\varrho_f} G + M \\
G : P_n &\xrightarrow{\varrho_b} G : P_n + M \\
M &\xrightarrow{\beta} M + P \\
M &\xrightarrow{\delta_M} \\
P &\xrightarrow{\delta_P} \\
P_i + P &\underset{\kappa_i^-}{\overset{\kappa_i^+}{\rightleftarrows}} P_{i+1} \qquad (1 \leq i \leq n-1)
\end{aligned}
$$

Dynamics of the Reaction System

$$
\begin{aligned}
\dot{G} &= \vartheta \cdot (\gamma_0 - G) - \alpha G P_n \\
\dot{M} &= \varrho_f G + \varrho_b \cdot (\gamma_0 - G) - \delta_M M \\
\dot{P} &= \beta M - \delta_P P + 2A_1 + A_2 + \cdots + A_{n-1} \\
\dot{P}_i &= -A_{i-1} + A_i \qquad (2 \leq i \leq n-1) \\
\dot{P}_n &= -A_{n-1} + \vartheta \cdot (\gamma_0 - G) - \alpha G P_n
\end{aligned}
$$

where

$$
A_i = \frac{1}{\varepsilon}\left(\kappa_{i+1}^{-} P_{i+1} - \kappa_{i+1}^{+} P_i P\right)
$$

Simplified Dynamics

Approximating

$$\dot{P} = \beta M - \delta_P P + n\big(\vartheta(\gamma_0 - G) - \alpha G P_n\big), \quad P_n = \bar{\alpha} P^n \quad \text{with} \quad \bar{\alpha} = \frac{\kappa_1^+ \cdots \kappa_{n-1}^+}{\kappa_1^- \cdots \kappa_{n-1}^-}$$

yields

$$\begin{aligned}
\dot{G} &= \vartheta \cdot \big(\gamma_0 - G\big) - \alpha\bar{\alpha} G P^n \\
\dot{M} &= \varrho_f G + \varrho_b \cdot \big(\gamma_0 - G\big) - \delta_M M \\
\dot{P} &= n\vartheta\big(\gamma_0 - G\big) - n\alpha\bar{\alpha} G P^n + \beta M - \delta_P P.
\end{aligned}$$

Many more simplifications yield

$$\begin{aligned}
\dot{G} &= \vartheta \cdot \big(\gamma_0 - G - G P^n\big) \\
\dot{M} &= \lambda G + \gamma_0 \mu - M \\
\dot{P} &= n\alpha \cdot \big(\gamma_0 - G - G P^n\big) + \delta \cdot \big(M - P\big).
\end{aligned}$$

Translation into First-Order Logic over the Reals

yields φ_n for fixed $n \in \mathbb{N}$.

$$\begin{aligned}\varphi_9 \;\doteq\; & \exists v_1 \exists v_2 \exists v_3 (v_1 > 0 \wedge v_2 > 0 \wedge v_3 > 0 \wedge \vartheta > 0 \wedge \gamma_0 > 0 \wedge \mu > 0 \wedge \delta > 0 \wedge \alpha > 0 \wedge \\ & \quad \vartheta(\gamma_0 - v_1 - v_1 v_3^9) = 0 \wedge \lambda v_1 + \gamma_0 \mu - v_2 = 0 \wedge \\ & \quad 9\alpha(\gamma_0 - v_1 - v_1 v_3^9) + \delta(v_2 - v_3) = 0 \wedge \\ & \quad \Delta_2 = 0 \wedge \Delta_1 > 0),\end{aligned}$$

where

$$\begin{aligned}\Delta_2 \;\doteq\; & 162\vartheta v_3^{17} \alpha v_1 + 162\vartheta\alpha v_1 v_3^8 + 162\alpha v_1 v_3^8 \delta + \vartheta + 2\vartheta v_3^9 \delta + \vartheta^2 v_3^{18} \delta + \vartheta v_3^9 \vartheta\delta \\ & + 81\alpha v_1 v_3^8 \vartheta\delta + 81\alpha v_1 v_3^{17} \vartheta\delta + \delta^2 + \vartheta\delta^2 + \vartheta^2\delta + \vartheta^2 + 2\vartheta^2 v_3^9 + \vartheta^2 v_3^{18} \\ & + 6561\alpha^2 v_1^2 v_3^{16} + 2\vartheta^2 v_3^9 \delta + \delta + 81\alpha v_1 v_3^8 + \vartheta v_3^9 \delta^2 - 9\lambda\vartheta v_1 v_3^8 \delta,\end{aligned}$$

$$\Delta_1 \;\doteq\; \vartheta\delta + \vartheta v_3^9 \delta + 9\lambda\vartheta v_1 v_3^8 \delta.$$

Hopf bifurcation for some $n \in \mathbb{N} \iff \varphi_n$ holds

Real Quantifier Elimination by Virtual Substitution

Principal Strategy

prenex formula, $\forall x_1 \varphi \longleftrightarrow \neg\exists x_1 \neg\varphi$,

$$\exists x_n \dots \exists x_2\, \exists x_1 \varphi \quad \longleftrightarrow \quad \exists x_n \dots \exists x_2\; \mathtt{simplify}\Big(\bigvee_{(\gamma,t)\in E} \gamma \wedge \varphi[x_1 /\!\!/ t] \Big).$$

$E = \{\dots, (\gamma, t), \dots\}$ is a finite **elimination set**

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$$ax^2 - 3x + 7 \leq 0 \ \rightsquigarrow\ \left(a \neq 0 \land (-3)^2 - 4 \cdot a \cdot 7 \geq 0,\ \frac{3 + \sqrt{(-3)^2 - 4 \cdot a \cdot 7}}{2 \cdot a} \right) \in E.$$

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More Generally
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$[x /\!\!/ t]$: atomic formulas $\longrightarrow$ quantifier-free formulas

Some Concrete Virtual Substitutions

Conventions: $f \in \mathbb{Z}[\mathbf{y}][x]$, f_i, g_i, $g_i^* \in \mathbb{Z}[\mathbf{y}]$

Quotients

$$\left(f_1 x + f_0 \leq 0\right)\left[x /\!/ \tfrac{g_1}{g_2}\right] \equiv f_1 \tfrac{g_1}{g_2} + f_0 \leq 0 \equiv f_1 g_1 g_2 + f_0 g_2^2 \leq 0$$

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Infinity

$$(f_2 x^2 + f_1 x + f_0 < 0)[x /\!\!/ \infty] \equiv f_2 < 0 \lor (f_2 = 0 \land f_1 < 0) \lor (f_2 = 0 \land f_1 = 0 \land f_0 < 0)$$

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Positive infinitesimals

$$(3x^2 + 6x - 3 > 0)[x /\!\!/ t - \varepsilon] \equiv 3t^2 + 6t - 3 > 0 \lor (3t^2 + 6t - 3 = 0 \land 6t + 6 \leq 0)$$

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Formal solutions of quadratic equations

$$\left(f = 0\right)\left[x /\!\!/ \frac{g_1 + g_2\sqrt{g_3}}{g_4}\right] \equiv \frac{g_1^* + g_2^*\sqrt{g_3}}{g_4^*} = 0 \equiv {g_1^*}^2 - {g_2^*}^2 g_3 = 0 \land g_1^* g_2^* \leq 0$$

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Košta 2016 (PhD thesis)

- method generalizes to higher degree bounds
- generic implementation with a degree bound of 3 is newly available

Some Complexity Results

Upper bound on asymptotic worst-case complexity

doubly exponential in the input word length (and this is optimal for the problem)

In the linear case

doubly exponential	in	# quantifier alternations
singly exponential	in	# quantifiers
polynomial	in	# parameters (= unquantified variables)
polynomial	in	# atomic formulas

particularly good for

low degrees and many parameters

For comparision: Cylindrical Algberaic Decomposition (CAD)

[Collins 1973, Arnon, Hong, Brown, . . .] doubly exponential in #all variables

Extended Quantifier Elimination

Generalize $\exists x\varphi \longleftrightarrow \bigvee_{(\gamma,t)\in E} \gamma \wedge \varphi[t /\!/ x]$ to $\exists x\varphi \rightsquigarrow \begin{bmatrix} \vdots & \vdots \\ \gamma \wedge \varphi[t /\!/ x] & x = t \\ \vdots & \vdots \end{bmatrix}$

A simple example

$$\varphi \equiv \exists x(ax^2 + bx + c = 0) \rightsquigarrow \begin{bmatrix} a \neq 0 \wedge b^2 - 4ac \geq 0 & x = \dfrac{-b - \sqrt{b^2 - 4ac}}{2a} \\ a = 0 \wedge b \neq 0 & x = -\dfrac{c}{b} \\ a = 0 \wedge b = 0 \wedge c = 0 & x = \infty_1 \end{bmatrix}$$

Semantics (for fixed parameters)

Whenever some left hand side condition holds, then $\exists x\varphi$ holds
and the corresponding right hand side term is **one** sample solution.

[M. Kosta, T.S., A. Dolzmann, J. Symb. Comput. 2016]

For fixed choices of parameters, standard values can be efficiently computed for all ∞_i and ε_i in a post-processing step.

Quantifier Elimination Results for Our Problem

- **Positive quantifier elimination** exploits positivity of all variables.
- Successful not on φ_n but on $\underline{\exists}\varphi_n$ ($n = 2, \dots, 10$):

n	$\underline{\exists}\varphi_n$	$\underline{\exists}\varphi_n[\lambda \leftarrow -\lambda]$	$\underline{\exists}\varphi_n[\lambda \leftarrow 0]$	time (s)
2	false	false	false	< 0.01
3	false	false	false	19.28
4	false	false	false	21.58
5	false	false	false	19.09
6	false	false	false	23.72
7	false	false	false	23.89
8	false	false	false	22.35
9	true	false	false	0.17
10	true	false	false	0.17

- **Extended positive QE** delivers also sample solutions, e.g., for $n = 9$:

$$\alpha = 1 \qquad \delta = 1 \qquad \gamma_0 = 0.0100554964908$$
$$\lambda = 17617230.5528 \qquad \mu = 0 \qquad \vartheta = 0.000211443608455$$
$$v_1 = 0.000000170287832189 \qquad v_2 = 3 \qquad v_3 = 1.24573093962$$

2012–2016

Hopf Bifurcations with Larger Models

Including MBO and MAPK

Switching to Convex Coordinates

In the previous example

- variables: concentrations of species
- parameters: reaction rates

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Stoichiometric network analysis (Clarke, 1980)

- We analyze system dynamics in flux space instead of concentration space.
- We represent the space of steady states with a combination of subnetworks.
- The subnetworks form a convex cone in flux space.
- Decomposing of the cone allows to search for lower dimensional facets (first).

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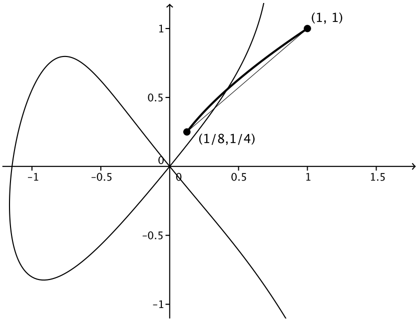
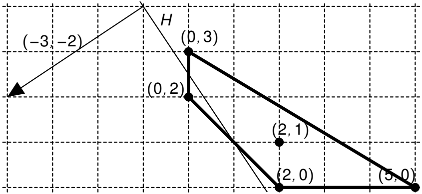
This gives us

- certain Hurwitz conditions $\Delta_{n-1} = 0$, $\Delta_{n-2} > 0$, $\Delta_{n-3} > 0$ for Hopf bifurcation,
- furthermore $\Delta_{n-4} > 0, \dots, \Delta_1 > 0$ for empty unstable manifold,
- and positivity conditions on the variables and parameters.
- The steady state approximation (vector field = 0) is not explicit anymore.
- One reaction yields many such problems of various dimensions (in flux space).
- Δ_{n-1} is generally much larger than the $\Delta_{n-2}, \dots, \Delta_1$.

An Incomplete Subtropical Decision Procedure





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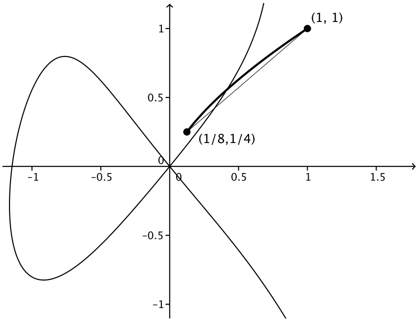

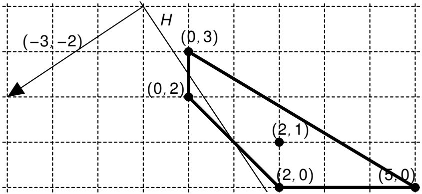

- $f = -2x_1^5 + x_1^2x_2 - 3x_1^2 - x_2^3 + 2x_2^2$
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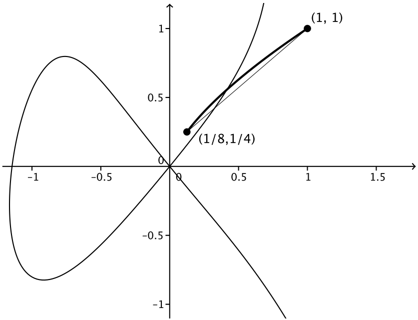

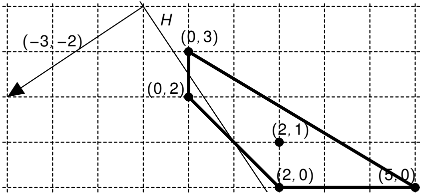

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  and use intermediate value theorem

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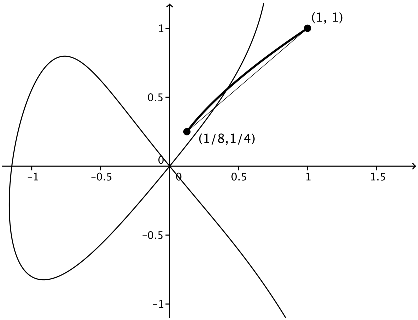

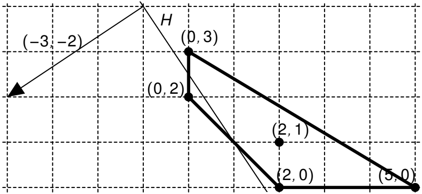

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Computation of a Positive Point

- $\mathrm{supp}^+(f) = \{(2, 1), (0, 2)\}$,

  $\mathrm{supp}^-(f) = \{(2, 0), (5, 0), (0, 3)\}$

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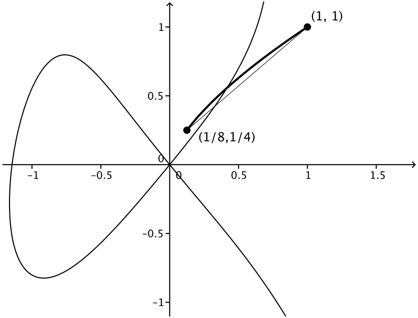

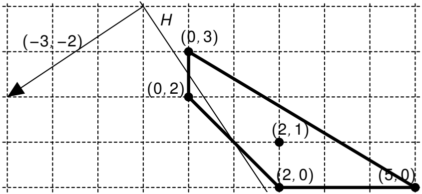

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- linear programming:
  $(0, 2) \in \mathrm{newton}(f) \cap \mathrm{supp}^+(f)$
  $(-3, -2)$ is normal of a separating hyperplane oriented towards $(0, 2)$

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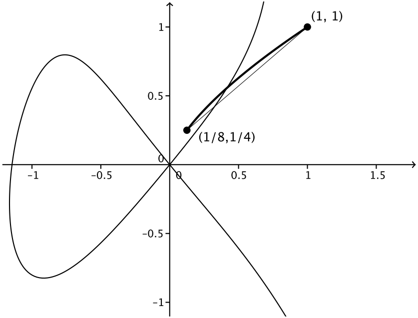

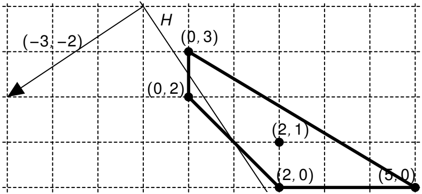

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  $(-3, -2)$ is normal of a separating hyperplane oriented towards $(0, 2)$
- positive point at (t^{-3}, t^{-2})

  for sufficiently large t

An Incomplete Subtropical Decision Procedure

$$f = -2x_1^5 + x_1^2 x_2 - 3x_1^2 - x_2^3 + 2x_2^2, \quad f(1,1) < 0 < f(2^{-3}, 2^{-2}) = f\left(\tfrac{1}{8}, \tfrac{1}{4}\right)$$

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Computation of a zero

$$\begin{aligned} -2x_1^5 + x_1^2 x_2 - 3x_1^2 - x_2^3 + 2x_2^2 &= 0 \\ x_1 &= \tfrac{1}{8} + y \cdot \left(1 - \tfrac{1}{8}\right) \\ x_2 &= \tfrac{1}{4} + y \cdot \left(1 - \tfrac{1}{4}\right), \qquad y \in]0, 1[\end{aligned}$$

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(1) $$\begin{aligned} \bar{f} &= f\left(\tfrac{1}{8} + y \cdot \left(1 - \tfrac{1}{8}\right), \tfrac{1}{4} + y \cdot \left(1 - \tfrac{1}{4}\right)\right) \\ &= (-16807y^5 - 12005y^4 - 934y^3 - 20778y^2 + 285y + 1087)/D, \quad D \in \mathbb{N} \end{aligned}$$

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$$\begin{aligned} -2x_1^5 + x_1^2 x_2 - 3x_1^2 - x_2^3 + 2x_2^2 &= 0 \\ x_1 &= \tfrac{1}{8} + y \cdot \left(1 - \tfrac{1}{8}\right) \\ x_2 &= \tfrac{1}{4} + y \cdot \left(1 - \tfrac{1}{4}\right), \qquad y \in \,]0, 1[\end{aligned}$$

(1) $\bar{f} = f\left(\tfrac{1}{8} + y \cdot \left(1 - \tfrac{1}{8}\right), \tfrac{1}{4} + y \cdot \left(1 - \tfrac{1}{4}\right)\right)$
$\quad = (-16807y^5 - 12005y^4 - 934y^3 - 20778y^2 + 285y + 1087)/D, \quad D \in \mathbb{N}$

(2) real root isolation yields $y \in \,]0.2, 0.3[$

An Incomplete Subtropical Decision Procedure

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(2) real root isolation yields $y \in\,]0.2, 0.3[$

(3) back-substitute real algebraic number $\langle \bar{f},]0.2, 0.3[\rangle$:

$$\begin{aligned}
x_1 &= \langle 686x^5 - 78x^3 + 584x^2 - 150x - 13,]0.32, 0.33[\rangle \\
x_2 &= \langle 16807x^5 - 12005x^4 + 2026x^3 + 9122x^2 - 4609x + 323,]0.42, 0.43[\rangle
\end{aligned}$$

An Incomplete Subtropical Decision Procedure

Some Details on the LP Part

$$\operatorname{supp}^+(f) = \{(2,1),(0,2)\} \quad \rightsquigarrow \quad B^+ = \begin{bmatrix} 2 & 1 & -1 \\ 0 & 2 & -1 \end{bmatrix}$$

$$\operatorname{supp}^-(f) = \{(2,0),(5,0),(0,3)\} \quad \rightsquigarrow \quad B^- = \begin{bmatrix} 2 & 0 & -1 \\ 5 & 0 & -1 \\ 0 & 3 & -1 \end{bmatrix}.$$

1. $\begin{bmatrix} -2 & -1 & 1 \\ 0 & 2 & -1 \\ 2 & 0 & -1 \\ 5 & 0 & -1 \\ 0 & 3 & -1 \end{bmatrix} \cdot (\mathbf{n}, c)^T \leq \begin{bmatrix} -1 \\ -1 \\ -1 \\ -1 \\ -1 \end{bmatrix}$ infeasible

2. $\begin{bmatrix} 0 & -2 & 1 \\ 2 & 0 & -1 \\ 5 & 0 & -1 \\ 0 & 3 & -1 \end{bmatrix} \cdot (\mathbf{n}, c)^T \leq \begin{bmatrix} -1 \\ -1 \\ -1 \\ -1 \end{bmatrix}$ feasible with $\mathbf{n} = (-3, -2)$ and $c = 5$

Methylene Blue Oscillator (MBO)

$$
\begin{array}{rcl}
MB^+ + HS^- & \longrightarrow & MB + HS \\
H_2O + MB + HS^- & \longrightarrow & MBH + HS + OH^- \\
HS + OH^- + MB^+ & \longrightarrow & MB + S + H_2O \\
H_2O + 2MB & \longrightarrow & MB^+ + MBH + OH^- \\
HS^- + O_2 & \longrightarrow & HS + O_2^- \\
HS + O_2 + OH^- & \longrightarrow & O_2^- + S + H_2O \\
H_2O + HS^- + O_2^- & \longrightarrow & HO_2^- + HS + OH^- \\
O_2^- + HS & \longrightarrow & HO_2^- + S \\
H_2O_2 + 2HS^- & \longrightarrow & 2HS + 2OH^- \\
MB + O_2 & \longrightarrow & MB^+ + O_2^- \\
HS^- + MB + H_2O_2 & \longrightarrow & MB^+ + HS + 2OH^- \\
OH^- + 2HS & \longrightarrow & HS^- + S + H_2O \\
MB + HS & \longrightarrow & MBH + S \\
H_2O + MBH + O_2^- & \longrightarrow & MB + H_2O_2 + OH^- \\
 & \longrightarrow & O_2
\end{array}
$$

Reduction to 6 dimensions with essential species O_2, O_2^-, HS, MB^+, MB, MBH

Application to the Methylene Blue Oscillator (MBO)

Characteristics of a typical input polynomial (among 496) for MBO:

- 7 variables
- degree in each variable between 4 and 9
- around 6000 summands (monomials)
- essentially irreducible

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Result Summary

- polynomial has zero: 30%
- polynomial has no zero: 67%
- incomplete method failed 3%
- computation time: 90 s on 60 cores (2.4 GHz Intel Xeon E5-4640)

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We did not observe any unsatisfied Hurwitz inequalities.

Application to a Single MAPK Layer

Model with 12 reactions and 9 species taken from Conradi et al. (2008)

Typical MBO Polynomial

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- $\sim$ 6000 monomials

Large MAPK Polynomial

- 10 variables
- degrees between 5 and 12
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- 5 s for exact solving (with real algebraic numbers)

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- 25 s for reading and parsing the polynomial into Reduce/Redlog
- 2 s for determining the degrees of the 10 variables
- 3000+ pages when printing in a LaTeX article

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But the Hurwitz determinant inequalities were never satisfied!

2016–

Parametric Saddle-node Bifurcations

with Another Model of MAPK

BIOMD0000000026 (MAPK)

$$
\begin{aligned}
\dot{x}_1 &= k_2 x_6 + k_{15} x_{11} - k_1 x_1 x_4 - k_{16} x_1 x_5 \\
\dot{x}_2 &= k_3 x_6 + k_5 x_7 + k_{10} x_9 + k_{13} x_{10} - x_2 x_5 (k_{11} + k_{12}) - k_4 x_2 x_4 \\
\dot{x}_3 &= k_6 x_7 + k_8 x_8 - k_7 x_3 x_5 \\
\dot{x}_4 &= x_6 (k_2 + k_3) + x_7 (k_5 + k_6) - k_1 x_1 x_4 - k_4 x_2 x_4 \\
\dot{x}_5 &= k_8 x_8 + k_{10} x_9 + k_{13} x_{10} + k_{15} x_{11} - x_2 x_5 (k_{11} + k_{12}) - k_7 x_3 x_5 - k_{16} x_1 x_5 \\
\dot{x}_6 &= k_1 x_1 x_4 - x_6 (k_2 + k_3) \\
\dot{x}_7 &= k_4 x_2 x_4 - x_7 (k_5 + k_6) \\
\dot{x}_8 &= k_7 x_3 x_5 - x_8 (k_8 + k_9) \\
\dot{x}_9 &= k_9 x_8 - k_{10} x_9 + k_{11} x_2 x_5 \\
\dot{x}_{10} &= k_{12} x_2 x_5 - x_{10} (k_{13} + k_{14}) \\
\dot{x}_{11} &= k_{14} x_{10} - k_{15} x_{11} + k_{16} x_1 x_5
\end{aligned}
$$

Values for the rate constants

$k_1 = 0.02$ $k_2 = 1$ $k_3 = 0.01$ $k_4 = 0.032$ $k_5 = 1$ $k_6 = 15$
$k_7 = 0.045$ $k_8 = 1$ $k_9 = 0.092$ $k_{10} = 1$ $k_{11} = 0.01$ $k_{12} = 0.01$
$k_{13} = 1$ $k_{14} = 0.5$ $k_{15} = 0.086$ $k_{16} = 0.0011$

BIOMD0000000026 (MAPK)

Steady-state-approximation and plugging in

$$
\begin{aligned}
-200x_1x_4 - 11x_1x_5 + 860x_{11} + 10000x_6 &= 0\\
500x_{10} - 16x_2x_4 - 10x_2x_5 + 5x_6 + 500x_7 + 500x_9 &= 0\\
-9x_3x_5 + 3000x_7 + 200x_8 &= 0\\
-10x_1x_4 - 16x_2x_4 + 505x_6 + 8000x_7 &= 0\\
-11x_1x_5 + 10000x_{10} + 860x_{11} - 200x_2x_5 - 450x_3x_5 + 10000x_8 + 10000x_9 &= 0\\
2x_1x_4 - 101x_6 &= 0\\
4x_2x_4 - 2000x_7 &= 0\\
45x_3x_5 - 1092x_8 &= 0\\
5x_2x_5 + 46x_8 - 500x_9 &= 0\\
-150x_{10} + x_2x_5 &= 0\\
11x_1x_5 + 5000x_{10} - 860x_{11} &= 0
\end{aligned}
$$

BIOMD0000000026 (MAPK)

Conservation laws

$$x_5 + x_8 + x_9 + x_{10} + x_{11} = k_{17}$$
$$x_4 + x_6 + x_7 = k_{18}$$
$$x_1 + x_2 + x_3 + x_6 + x_7 + x_8 + x_9 + x_{10} + x_{11} = k_{19}$$

Some realistic values for those new constants

$$k_{17} = 100 \qquad k_{18} = 50 \qquad k_{19} \in \{200, 500\}$$

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Saddle-node Bifurcation

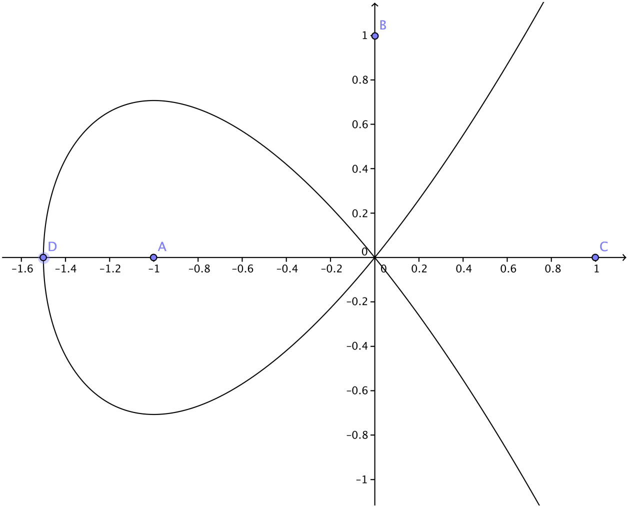
The number of solutions for $x_1, \ldots, x_{11}$ changes from unique to non-unique.

Cylindrical Algebraic Decomposition

$\varphi(f_1, f_2)$ is a Boolean combination of constraints with left hand sides f_1, f_2 and right hand sides 0.

$f_1(x, y) = 2y^2 - 2x^3 - 3x^2$

$f_1(A) = -1 < 0$
$f_1(B) = 2 > 0$
$f_1(C) = -5 < 0$
$f_1(D) = 0$



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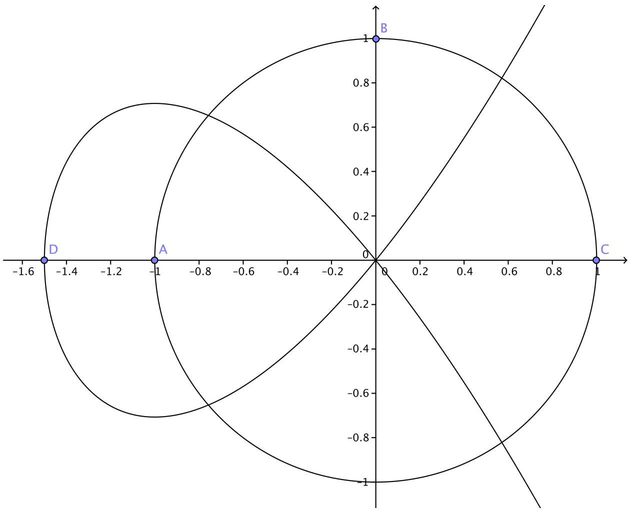
$f_2(x, y) = y^2 + x^2 - 1$



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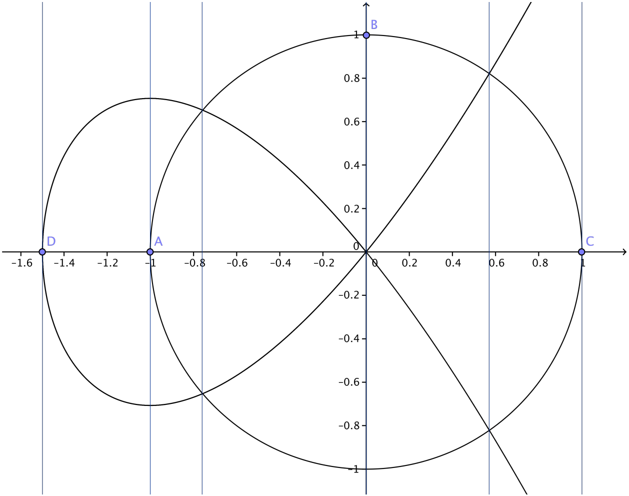

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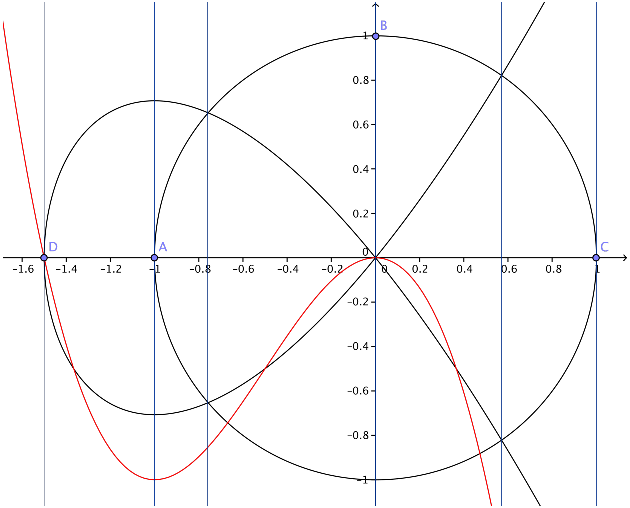
$f_2(x, y) = y^2 + x^2 - 1$

$g(x) = -2x^3 - 3x^2$
...
projection polynomials



Application of CAD to Our MAPK Model

First Without Parameters

Recall $k_{17} = 100$, $k_{18} = 50$, $k_{19} \in \{200, 500\}$; **plug in** k_{17}, k_{18}.

For $k_{19} = 200$:

$$x^{(200)} = (90.6, 2.6, 10.4, 17.8, 35.9, 32.0, 0.0, 15.5, 2.3, 0.6, 45.4)$$

For $k_{19} = 500$:

$$x_1^{(500)} = (17.6, 6.9, 367.5, 36.6, 5.5, 12.8, 0.5, 83.4, 8.0, 0.2, 2.7)$$
$$x_2^{(500)} = (122.0, 14.6, 234.9, 14.5, 7.1, 35.0, 0.4, 69.4, 7.4, 0.7, 15.2)$$
$$x_3^{(500)} = (323.7, 9.4, 37.1, 6.7, 13.6, 43.1, 0.1, 20.8, 3.2, 0.8, 61.4)$$

- Float approximations for convenience — we have exact real algebraic numbers

Application of CAD to Our MAPK Model

Now with Parametric k_{19}

- Eliminate $x_1, x_3, \ldots, x_{11}$ by virtual substitution.
- Then CAD with variables k_{19} and x_2
- For all $k_{19} > 0$ there is at least one positive solution for x_2
- The system changesfrom one to three solutions around $k_{19} = 409.3$.

Application of CAD to Our MAPK Model

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- The system changesfrom one to three solutions around $k_{19} = 409.3$.

The exact break point

is the only real zero in the interval $(409, 410)$ of $\sum_{i=0}^{10} c_i k_{19}^i$ with

$$
\begin{aligned}
c_{10} &= 351590934502740290936895033267017158736060313940693076650155371250411 \\
c_9 &= -213699072852157674283997527746395583273033983170426080574800781989093156 \\
c_8 &= 25374851641220554774259605635053469432582109883965015804077119110958034090 \\
c_7 &= 12972493018300022707027639267804259251235991618029852880330004508564391594000 \\
c_6 &= -8468945963692802414226427249726123493448372439778349029355636316929687020660000 \\
c_5 &= 2231098270337406450670301663172664333421440833875848621423683265663846533079600000 \\
c_4 &= -376265008904112258290319173193792052014899485528994925965885895511831873444245100000 \\
c_3 &= 39262101548790869407057994985320156500968958361396178908180026842806643766783104000000 \\
c_2 &= -24926239907430292349743540812702961063096034624515170577798775968424482877993376000000000 \\
c_1 &= 709788507358874734591769971861759784258732672467600232129406169246431718684780800000000000 \\
c_0 &= -10628711928389858769480771149238982049904341389014953948347496131846703628103680000000000000
\end{aligned}
$$

The Combined System Once More

$$
\begin{aligned}
-200x_1x_4 - 11x_1x_5 + 860x_{11} + 10000x_6 &= 0\\
500x_{10} - 16x_2x_4 - 10x_2x_5 + 5x_6 + 500x_7 + 500x_9 &= 0\\
-9x_3x_5 + 3000x_7 + 200x_8 &= 0\\
-10x_1x_4 - 16x_2x_4 + 505x_6 + 8000x_7 &= 0\\
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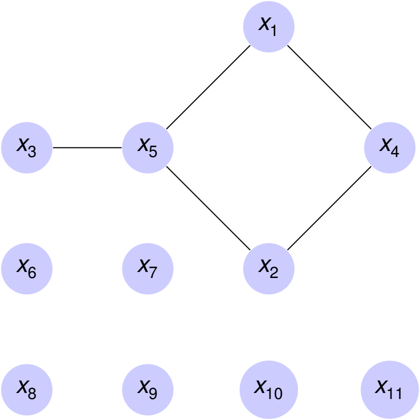
11x_1x_5 + 5000x_{10} - 860x_{11} &= 0\\
-k_{17} + x_{10} + x_{11} + x_5 + x_8 + x_9 &= 0\\
-k_{18} + x_4 + x_6 + x_7 &= 0\\
-k_{19} + x_1 + x_{10} + x_{11} + x_2 + x_3 + x_6 + x_7 + x_8 + x_9 &= 0
\end{aligned}
$$

A Minimum Vertex Cover



This Yields

$$
\begin{aligned}
1062444k_{18}x_4^2x_5 + 23478000k_{18}x_4^2 + 1153450k_{18}x_4x_5^2 + 2967000k_{18}x_4x_5 \\
+ 638825k_{18}x_5^3 + 49944500k_{18}x_5^2 - 5934k_{19}x_4^2x_5 - 989000k_{19}x_4x_5^2 \\
- 1062444x_4^3x_5 - 23478000x_4^3 - 1153450x_4^2x_5^2 - 2967000x_4^2x_5 \\
- 638825x_4x_5^3 - 49944500x_4x_5^2 &= 0
\end{aligned}
$$

$$
\begin{aligned}
1062444k_{17}x_4^2x_5 + 23478000k_{17}x_4^2 + 1153450k_{17}x_4x_5^2 + 2967000k_{17}x_4x_5 \\
+ 638825k_{17}x_5^3 + 49944500k_{17}x_5^2 - 1056510k_{19}x_4^2x_5 - 164450k_{19}x_4x_5^2 \\
- 638825k_{19}x_5^3 - 1062444x_4^2x_5^2 - 23478000x_4^2x_5 - 1153450x_4x_5^3 \\
- 2967000x_4x_5^2 - 638825x_5^4 - 49944500x_5^3 &= 0
\end{aligned}
$$

- We managed to compute a CAD with 2 parameters.
- Also a real triangularization
- This is where we are standing right now.

The story continues …